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(54) COMPRESSED AND FORMED ALKALINE COMPONENT SUITABLE FOR USE IN BUFFERED ACETYLSALICYLIC ACID PRODUCT

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ABSTRACT OF THE DISCLOSURE

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A compressed and formed alkaline component suitable for use in a buffered acetylsalicylic acid product. The alkaline component is made of alkaline materials selected from the group consisting of calcium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide and mixtures thereof and having incorporated therein citric acid and monobasic sodium phosphate.

COMPRESSED AND FORMED ALKALINE COMPONENT SUITABLE FOR USE IN BUFFERED ACETYLSALICYLIC ACID PRODUCT

This invention relates to alkaline components for buffered acetylsalicylic acid (ASA) products. More particularly, it concerns alkaline components of the above type which are characterized by an improved rate of reaction with acid that is present in the stomach when such products are administered to a subject. The novel combined alkaline component-ASA products of this invention have utility as analgesics and/or antipyretics that are commonly ascribed to ASA products.

Buffered ASA products; that is, ASA products that are formulated so as to simultaneously deliver alkaline material and ASA to the stomach has been known for a long time. The alkaline materials are administered simultaneously with ASA , among other reasons, in order to reduce the acidity of the stomach content during this administration and at the same time, react with ASA to form a soluble salt. In this fashion, it is hoped that the potential of ASA for gastric irritation and bleeding may be reduced.

The reduction of the acidity in the stomach brought about by the alkaline material is essentially due to the neutralization reaction that takes place between the alkaline material and the acid content of the stomach. Any factor which would increase the rate of this reaction would tend to increase the beneficial effect of the alkaline material when administered with ASA.

It is customary in the simultaneous administration of alkaline material and ASA to separate the alkaline material from the ASA in the unit dosage form. This may take the form of a multi-layered tablet in which the

alkaline material is formed into one layer and the ASA in another layer. In another dosage form, the alkaline layer may be formed into a small tablet or pellet and the ASA may be delivered as a powder or granulation. In this case, the small tablet might be loaded into a capsule followed by the powdered or granulated ASA material. In each of the aforesaid cases, the alkaline material is usually prepared as a granulation and then compressed into a form. In the first case, the form takes the shape as a layer of a multi-layered tablet. In the second case, it takes the form of a discrete tablet or pellet.

It has now been found that the rate of reaction of the alkaline material in the aforesaid compressed forms with the acid content of the stomach can be increased if in shaping said alkaline forms, a combination of citric acid and monobasic sodium phosphate (NaH_2PO_4) is incorporated in the alkaline composition. The citric acid and the monobasic sodium phosphate will usually be added in the form as a component of the granulating liquid or solution. Moreover, best results are obtained with alkaline materials selected from the group consisting of magnesium carbonate, calcium carbonate, magnesium oxide, magnesium hydroxide and combinations thereof. Of special interest are the following combinations of alkaline materials (1) MgO and $CaCO_3$; (2) $Mg(OH)_2$ and $CaCO_3$; (3) MgO, $MgCO_3$ and $CaCO_3$; (4) $Mg(OH)_2$, $MgCO_3$ and $CaCO_3$; (5) $MgCO_3$ and $CaCO_3$; and (6) MgO and $Mg(OH)_2$.

It is accordingly an object of the present invention to provide a compressed and shaped alkaline component for a buffered ASA product which increases the rate of

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reaction of said alkaline component with the acid content of the stomach.

It is also an object of this invention to provide a process for alleviating pain and/or fever in a subject by administering to said subject the product of the foregoing object.

Other and more detailed objects of this invention will be apparent from the following description and claims.

Although the formed compressed alkaline component of the present invention may be used in conjunction with ASA in a variety of modes (e.g. as multi-layered tablets) for convenience of description, emphasis for the most part will be placed on those dosage forms in which the alkaline component is formed into at least one discrete tablet or pellet which is then loaded into a capsule along with a powdered or granulated ASA mix.

This mode of the present invention provides capsules containing analgesic compositions in which the active analgesic ingredient is normally unstable. ASA may be the sole active analgesic ingredient. However, other active analgesics in addition to ASA as well as, other pharmaceutically active ingredients with or without non-ASA analgesics may be contained in the capsule.

The small alkaline tablet which forms part of the analgesic product of this mode of the present invention will contain a combination of the alkaline materials mentioned above. In addition, it may also contain other ingredients which are compatible with the alkaline material in the tablet.

As used herein, the term "ASA mixture" refers to

that powder and/or granular portion of the composition that contains the ASA but may also contain other compatible powder or granular materials. The term "alkaline tablet" refers to the small tablet which contains the alkaline material but may also contain other compatible ingredients.

The term "magnesium oxy component" as used in the present specification means a material selected from the group consisting of magnesium oxide, magnesium hydroxide or a combination of magnesium oxide and magnesium hydroxide.

Unless otherwise specified, percent is given as percent by weight based on the total weight of the product contained in the dosage form.

ALKALINE TABLET

The alkaline tablet used in this mode of the invention is a small tablet dimensioned so that it can be conveniently dropped into the open end of a capsule which is of a suitable size for use in this invention e.g. #0, #1 and #2. The capsules can be either hard shell or soft shell gelatin capsules, with hard shell preferred. The alkaline tablets will usually comprise the combination of alkaline materials described above that are formed into a granulation by a wet granulation process to provide a material that is readily compressible to form a tablet.

The wet granulation process will usually involve preparing a granulating liquid comprising an aqueous vehicle having dissolved therein citric acid and monobasic sodium phosphate. The quantity of these ingredients contained in the granulating liquid may vary somewhat; usually, however, they will fall within the following percent ranges based on the total weight of the granulating liquid:

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citric acid from about 1% to about 5%; monobasic sodium phosphate from about 1% to about 5%. Other ingredients commonly contained in a granulating liquid may also be contained in the granulating liquid employed in this invention.

In preparing the alkaline granulation, the granulating liquid containing the citric acid and monobasic sodium phosphate is mixed with the alkaline mix described in more detail below. This is then passed through a screen having suitable size openings to form granules which are then dried. The granules so formed are then passed through an oscillating screen of suitable size to provide granules that can be compressed into an alkaline tablet.

The quantity of citric acid and monobasic soidum phosphate that will be contained in the alkaline tablet or other similar formed and compressed alkaline component will vary somewhat. Usually, this will be within the following ranges based on the total weight of said alkaline component: citric acid from about 1% to about 5%; monobasic sodium phosphate from about 1% to about 5%.

The total quantity of alkaline material as a combination of the alkaline ingredients mentioned above may vary somewhat as long as they can be formed into a suitable alkaline sized tablet. The total amount of alkaline material is usually related to the amount of ASA contained in the ASA component. Typically, the amount of alkaline material is present in the tablet at a level of from about 20% to about 150% by weight based on the weight of ASA contained in each capsule. The quantity employed will depend on the acid consuming capacity (ACC value) of the alkaline material.

To get the full benefit of the alkaline component insofar as it has an effect on the absorption rate of the ASA, it is important that the alkaline tablet have a

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fast disintegration rate. Good disintegration rates are obtained where the alkaline material consists of a combination of magnesium carbonate, calcium carbonate and the magnesium oxy component as defined above.

The quantity of alkaline material contained in the compressed alkaline component of this invention may vary somewhat. As used herein, the term alkaline component refers to the formed and compressed alkaline section of the dosage forms. This includes the separate alkaline tablet or tablets that are to be included in a capsule along with ASA or it may be a layer of a multi-layered tablet. The formed and compressed alkaline component ordinarily will contain other ingredients besides alkaline materials.

Usually, the quantity of alkaline material that will be contained within the alkaline component will comprise between about 35% to about 95% by weight based on the total weight of the compressed and formed alkaline component. Most often, however, alkaline material will constitute between about 75% to about 95% on the same weight basis.

The relative amounts of calcium carbonate, magnesium carbonate and magnesium oxy component that will be contained in the compressed and formed alkaline component may also vary. This will largely be determined by the acid consuming capacity requirement for the particular dosage form. Generally, calcium carbonate, when present, will comprise up to 95% by weight of the compressed and formed alkaline component but most often this will not exceed 75% on the same weight basis. Similarly, when magnesium carbonate is utilized, this will ordinarily not exceed 95% by weight of said alkaline component. Again, usually this will not exceed 35% on the same weight basis.

The magnesium oxy component in the form of magnesium oxide, magnesium hydroxide or combinations of magnesium oxide

and magnesium as indicated above may constitute the sole alkaline material contained in the alkaline component or may be employed in conjunction with the other alkaline materials. When it constitutes all or a part of said alkaline component, it may be used at a level up to and including about 95% by weight based on the weight of said alkaline component. However, this will ordinarily not exceed about 75% by weight on the same weight basis.

In the preferred form of this invention, all three types of alkaline materials i.e. calcium carbonate, magnesium carbonate and magnesium oxy component are used simultaneously. In this case, the percent ranges for the respective alkaline materials based on the total weight of the compressed and formed alkaline component are as follows:

calcium carbonate	from about 20% to about 75%
magnesium carbonate	from about 5% to about 35%
magnesium oxy component	from about 10% to about 75%

The magnesium oxy component may be added to the pre-granulation alkaline mix as magnesium oxide, magnesium hydroxide or as a combination of magnesium oxide and magnesium hydroxide. Since the granulation step involves wetting the pre-granulation mix with an aqueous granulating liquid when magnesium oxide is used, some part or all of the magnesium oxide may be converted into magnesium hydroxide.

It is also advantageous to incorporate a disintegrant in the alkaline tablet of the present product to increase the rate at which it disintegrates in the stomach. A variety of materials are known in the tabletting art which will accomplish this function. These include such materials as

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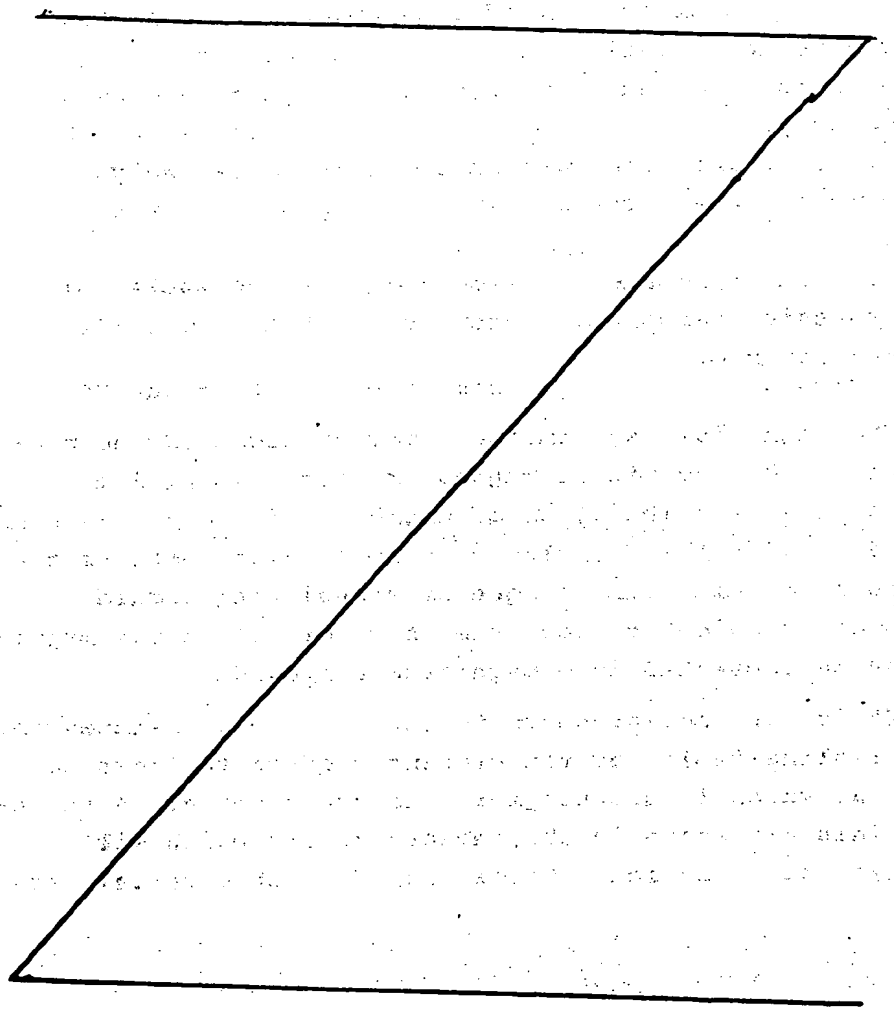
corn starch, potato starch, wheat starch, modified starch (e.g. Sta-Rex*) and sodium carboxymethyl starch (e.g. Primojel*). Ordinarily, such materials are present in the alkaline tablet at a level in the range of from about 5% to about 25% by weight based on the total weight of the alkaline tablet.



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* Trademarks.

Other ingredients may be added to the alkaline tablet to improve its physical or organoleptic characteristics or to facilitate the manufacture of the alkaline tablet. A lubricant such as magnesium stearate, stearic acid or silicone fluid may be added to facilitate the tabletting of the alkaline granulation.

The alkaline tablet is dimensioned so that it will contain a maximum amount of weight of material in a minimum volume so it can be readily dropped into a gelatin capsule e.g. #0 gelatin capsule. This is accomplished by forming the alkaline tablet as a spheroid or near-spheroid having a diagonal dimension of no greater than the diameter of the open end of the capsule. Usually, the diameter of the tablet at its greatest dimension will be in the range of from about 0.225" to about 0.255" for #0 gelatin capsule. For different sized capsules, the appropriate diameter tablet will be used.

Because of the difficulty in compressing a granulation into a true spheroidal tablet in the preferred practice of this invention, a modified deep ball punch is employed. This gives a modified spheroidal tablet having the form of a solid cylinder provided with an upper and lower dome. In this case, the important dimension is the diameter of the tablet in longitudinal cross section that extends from the top of one vertical side to the bottom of the other vertical. A suitable diameter is in the range of from about 0.210" to about 0.255" for #0 gelatin capsule. The punch size will be changed for different gelatin capsule size so that the weight of the tablet and the diameter of the tablet will be reduced proportionally to satisfy the ACC meq. alkalinity to the q.s. ASA used.

ASA MIXTURE

The principal ingredient on a weight basis in the ASA mixture will usually be ASA. This will ordinarily take the form of a powder or dry granulation that may vary widely in particle size. In the typical cases, this will usually fall within the range of from about 100% which pass through a 12 mesh screen to about 100% which pass through a 80 mesh screen. "Micronized" ASA well known to those skilled in this art may also be used.

The lower limit of ASA which will be contained in the capsule of this invention will be about 81 mg. for pediatric use. For adults, this will usually be about 325 mg. The upper limit is limited only by the feasibility of swallowing the size of the capsule that is required to contain this material. As a practical matter, this will rarely exceed about 650 mg. of ASA per capsule. For the usual adult use, between 325 mg. to 500 mg of ASA will be contained in each capsule. In the preferred embodiment, the ASA level will be about 500 mg/capsule. The ordinary single dose will be one or two capsules for adults.

The ASA mixture may also contain conventional excipients which are compatible with ASA and which are well known to those skilled in the pharmaceutical arts such as, for example, starch, modified starch (e.g. product sold under the trade mark "Sta-Rx"*), microcrystalline cellulose (Avicel* or Elcema*), sodium carboxymethyl starch (Explotab*, Primojel*).

The quantity of excipient in each capsule can vary depending upon the quantity of ASA contained therein and the size of the capsule. Typically, the quantity of excipient in each capsule is within the range of from about

* Trademarks

0% to about 50% by weight based on the weight of the ASA contained in the mixture.

The ASA mixture may also contain a lubricant which serves to facilitate the flow of powder or granular materials during filling and processing. There are a number of lubricants well known to those skilled in this art that may be employed. For example, mention may be made of the Silicone Fluids (i.e. polydimethylsiloxane), fumed silicone dioxide (e.g. Cab-O-Sil* M-5 or Aerosil* 200), light mineral oil, and polyethylene glycol (Carbowax* 400), etc.

The quantity of lubricant in the ASA mixture is related to the quantity of ASA present. Typically, the quantity of lubricant in each capsule is within the range of from about 0.1% to about 5% by weight based on the weight of the ASA contained in the mixture.

In addition to ASA other pharmaceutically active ingredients may be contained in the ASA mixture. These may be other analgesics, analgesic potentiators, antihistamines, decongestants, and antitussive agents. By way of illustration of such other pharmaceutically active ingredients, mention may be made of acetaminophen, caffeine, chlorpheniramine maleate, phenylpropanolamine HCl, dextromethorphan, codeine, doxylamine succinate, phenindamine tartate and other salts thereof and surfactants such as sodium lauryl sulfate, polyvinyl-pyrrolidone, polyoxyethylene(20)sorbitan monooleate (Tween* 80), etc.

After the alkaline tablets are formed, they are fed to a filling station where each is inserted into the body of a capsule and the capsule containing the alkaline tablet is passed on to a second station where it receives

* Trademarks.

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the powdered ASA mixture. After receiving the powdered ASA mixture, the capsule is capped with the upper half of the capsule and the product is completed.

The capsules that are employed in the present invention may be conventional gelatin capsules that are well known to those skilled in this art. These may vary somewhat in size but usually they will be #0, #1, #2 and #3. Since a fast rate of absorption of ASA into the bloodstream is a desirable feature, it is advantageous to employ a capsule which in itself is fast dissolving. With this in mind, it is useful to include in the gelatin material that constitutes the capsule about 10% by weight of calcium carbonate based on the total weight of the capsule mentioned.

As indicated above, the formed alkaline component of this invention may form part of a multi-layered tablet also containing ASA. A typical case of this character is a two-layered tablet in which the alkaline granulation described above in preparing the "alkaline tablet" may be used in forming one layer of the tablet and the "ASA mixture" also described above is used to form the ASA layer of such a two-layered tablet. The technique for making the two-layered tablets is well known to those skilled in this art. In general, this involves feeding a measured quantity of the ASA granulation into a tablet punch, optionally tamping the ASA granulation down to form a first layer, feeding a measured quantity of the alkaline granulation into said tablet punch to cover said ASA layer and to form a second layer and then compressing the layers together.

The following Examples are given to further illustrate the present invention. It is to be understood, however, that the invention is not limited thereto.

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EXAMPLE 1

Formula RF #2034 (Capsule)

Dosage Unit Amount mg/tablet	Item No.	Ingredients	Gms/10,000 Tablets
PART I: A) Alkaline Granulation			
38.24	1	Magnesium oxide U.S.P. heavy	382.4
23.90	2	Magnesium carbonate U.S.P.	239.0
95.60	3	Calcium carbonate U.S.P. heavy **	956.0
2.39	4	Citric Acid, anhy. powder	23.9
2.39	5	Monosodium phosphate, anhy. (NaH_2PO_4)	23.9
q.s. to dissolve 4 & 5	6	Water, deionized	q.s. to dissolve 4 & 5
2.87	7	Starch, corn	28.7
q.s. to suspend 7	8	Water, deionized	q.s. to suspend 7
16.25	9	Starch, corn	162.5
181.64			1816.4
B) Alkaline Tablet			
181.64	10	(A) Alkaline Granulation	1816.4
Range 0.36-0.72++	11	Magnesium stearate, U.S.P.	3.6
182.00			1820.0

Procedure:

A) Alkaline Granulation -

a. In ribbon blender charge 1, 2 and 3. Mix for 5 minutes.

b. Dissolve 4 and 5 in 6 at 100°C.
c. Suspend 7 in 8 and add to (b) while agitating (1 minute).
d. Add hydrolyzed starch (b,c) to (a) and mix for 3-5 minutes.
e. Add 9 to (a) mix another 1-2 minutes.
f. Pass (e) through Tornado Mill with a 3/4" screen.
g. Dry in Fluid Bed Dryer (inlet temp. 8-90°C) outlet temp. 35-36°C) to a moisture of 1-2% maximum.
h. Pass (g) through oscillator with a 10 mesh screen.

B) Alkaline Tablet -

a. In a V-blender mix 10 & 11 for 15 minutes.
b. Compress to the specifications below:

Appearance: White spherical tablet
Taste,odor: Alkaline taste
Moisture: Part A - 1-2% max.
ACC meq. 4.3 per tablet
Punch: 7/32" special spherical punch
Weight: 182 mg.
Thickness++: .210"-.230" (cup depth 0.050"-0.057")
Disintegration: USP Basket App., Water 37°C - 10-30 sec.
Diagonal Measurement .260"
Tablet Wt.: 182 mg $\pm$ 5%

Dosage Unit Amount mg/capsule	Item No.	Ingredients	Prepared for 200,000 capsules Gms/4,440
PART II: A)		Excipient and Lubricant	
21.20 Range 10-30	1	Modified starch 1500 Sta-Rx 1500*	4,000 (Before drying 4,240)
2.00 Range 2-5	2	Dimethylpolysiloxane Fluid 360 Medical Type/350 centistokes	400
0.20	3	Polyoxyethylene(20) sorbitan monooleate (Tween 80)*	40
23.40			4,440
B)		ASA Mixture	
500.00	4	ASA 80 mesh	100,000
22.20	5(A)	Excipient & lubricant	4,440
522.20			104.440

Procedure

A) Excipient and Lubricant -

a. Place 1 in a mixer and add 2 and 3 (previously mixed). Mix for 5 minutes.

b. Dry (a) in a Fluid Bed Dryer (inlet temp. 80°C - outlet temp. 55-60°C) approx. 15 minutes.

B) ASA Mixture -

a. In a Ribbon blender, charge 4 and 5. Mix for 15 minutes.

b. Pass (a) through oscillator with an 8 mesh screen.

OR -

1) a. Dry Sta-Rx* in oven at 40-50°C to 4% maximum moisture.

b. In Ribbon blender, mix Sta-Rx* and ASA for 5 minutes. Then add premixed silicone

* Trademarks.

fluid and Tween*80, mix another 5 min. Pass through #8 mesh screen.

2) a. Buy dry Sta-Rx* 4% maximum moisture.
b. Same as (1 b)

Appearance: White oily powder
Taste,Odor: Slight Tween* odor
Moisture A) Excipient & Lubricant 4% max. (Range 1-4%)

Capsule Filling Procedure:

Alkaline tablets prepared in accordance with the procedure described above in Part I (A) and (B) are inserted into capsules (capsule size #0) with an automatic filler. The ASA mixture prepared in accordance with the procedure described above in Part II (A) and (B) is fed to a hopper and is used to load the capsule in accordance with the following specifications:

Ingredients	mg/capsule	
ASA	500.00	
Excipient	22.20	± 5%
Alkaline Tablet	182.00	
Empty caps.	100.00	
	804.20	

Range: 764 mg - 844 mg

* Trademarks.

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EXAMPLE 2

Formula 1565-73 (Capsule)

Alkaline Tablet -

Ingredients	mg/tablet	gms/batch
Magnesium oxide	40	1600
Magnesium carbonate	25	1000
Calcium carbonate	100	4000
Starch	20	800
Citric Acid	2.5	100
NaH_2PO_4	2.5	100
	190.0	7600

Moisture less than	1%
Add Magnesium stearate	0.38
	190.38

Disintegration: 10-20 seconds
Thickness: .215" - .220"
ACC value = 4.5 meq

ASA Mix -

Ingredients	mg/tablet
ASA (80 mesh)	450.
ASA (micronized)	50.
Sta-Rx* (starch)	20.
Silicone fluid	2.
Tween 80*	.30
	522.30

* Trademarks.

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Using automatic or semi-automatic filling equipment #0 gelatin capsules were filled with one alkaline tablet each and the specified amount of ASA mix. Each capsule had the following specifications:

Alkaline tablet	190.38 mg.
ASA mix	522.30 mg
Total composition	712.68 mg ± 3%
Empty caps.	100.00 mg.
Total Product Weight	812.68 mg.

EXAMPLE 3

Formula 1565-82 (Capsule)

Alkaline Tablet -

Ingredients	mg/tablet
Magnesium hydroxide	65
Magnesium carbonate	25
Calcium carbonate	78 Sturcal* H
Citric acid	2.5
NaH_2PO_4	2.5
Starch	3
Starch	17
	173

Moisture: 1.5%

Alkaline granulation: 193

Magnesium stearate: 0.386

193.386

Weight: 0.193.38

Thickness: 0.235"

Diagonal: 0.250" ± .005

Disintegration time: 10-30 sec.

* Trademark.

Alkaline tablets made in accordance with the above formula and specifications may be loaded into #0 gelatin capsule, one tablet for each capsule. The aspirin mix described in Example 2 may then be loaded into each capsule in the measured quantity also specified in Example 2 and then the capsule is capped.

EXAMPLE 4

Formula CL 1565-85 (Capsule)

(A) ASA Mix

Ingredients	mg/capsule
ASA 80 crystals	325.
Sta-Rx*(dry)	14.
Silicone Fluid 360	1.4
Tween 80*	0.15
	340.55

(B) Alkaline Tablet

Same as alkaline tablet of Example 1.

Two alkaline tablets, as described in Example 1, each weighing about 183 mg were prepared from the alkaline mix and placed in an empty #0 gelatin capsule. The aspirin mix is then added to specifications and the cap of the capsule is applied.

*Trademarks.

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EXAMPLE 5

Formula CL 1565-84A (Two-Layered Tablet)

	Ingredients	mg/tablet
(A)	**ASA Layer**	
	ASA 12/50 (granulation containing 10% Starch)	362.
(B)	**Alkaline Layer**	
	Alkaline mixture of Example 1 before compression into tablet (Formula RF# 2034)	300.
		662.

This tablet had a thickness of within .205-.210 and an ACC value of 7.0 meq.

EXAMPLE 6

Formula CL 1565-84B (Two-layered Tablet)

	Ingredients	mg/tablet
(A)	**ASA Layer**	
	ASA 12/50 (granulation containing 10% Starch)	362.
(B)	**Alkaline Layer**	
	Alkaline mixture of Example 1 before compression into tablet (Formula RF #2034)	360.
		722.

This tablet had a thickness of from .45" - .220" and an ACC value of 8.5 meq.

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EXAMPLE 7

Formula CL 1565-84C (Two-layered tablet)

The same as Example 6, except that tablet had a thickness of .230".

EXAMPLE 8

Formula CL 1565-84D (Two-layered tablet)

The same as Example 6, except that tablet had a thickness of .235" - .240".

EXAMPLE 9

Formula CL 1565-84E (Two-layered tablet)

The same as Example 6, except that tablet had a thickness of .245".

EXAMPLE 10

Formula CD 1854-23 (Two-layered tablet capsule shape)

LAYER I	
Ingredients	mg/tablet
ASA 12/50 (granulation containing 10% starch)	555.5
LAYER II	
Magnesium oxide	63.87
Magnesium carbonate	39.92
Calcium carbonate	159.68
Citric acid	3.99
Monosodium phosphate	3.99
Corn Starch, Part I	4.79
Corn Starch, Part II	27.15
Magnesium stearate	0.61
	304.00
	859.5

ACC value: 7.18 meq.

Compressed on Stokes Rotary press equipped with capsule shaped punches.

EXAMPLE 11

Formula 1595-183 (Two-layered tablet)

	Ingredients	mg/tablet
	LAYER I	
	ASA starch granulation 12/50 (ASA 7 1/2 gr)	541.7
	LAYER II	
	Magnesium oxide	88.96
	Magnesium carbonate	55.60
	Calcium carbonate	222.40
	Citric acid	5.56
	Monosodium phosphate	5.56
	Corn Starch, Part I	6.67
	Corn Starch, Part II	37.81
	Magnesium stearate	0.84
		423.4
		965.1

ACC value: 10 meq.

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EXAMPLE 12

Formula 1595-182 (Two-layered tablet)

LAYER I Ingredients	mg/tablet
ASA starch granulation 12/50 (ASA 7 1/2 gr)	541.7
LAYER II	
Magnesium oxide	63.87
Magnesium carbonate	39.92
Calcium carbonate	159.68
Citric acid	3.99
Monosodium phosphate	3.99
Corn Starch, Part I	4.79
Corn Starch, Part II	27.15
Magnesium stearate	0.61
	304.00
	845.7

ACC value: 7.2 meq.

To compare the relative speed of reaction of the formed alkaline component of the present invention containing the citric acid and monobasic sodium phosphate with one in which these components are absent, the following in vitro experiments were carried out. Alkaline tablets having the formulas set out below were prepared:

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Formula CL 1565-83A

Alkaline Tablet:

Ingredients	mg/tablet
Magnesium carbonate	23.90
Calcium carbonate (Sturcal H)	95.60
Magnesium oxide	38.24
Starch	19.12
	176.86
Magnesium stearate	0.35
	177.21

Formula CL 1565-83B

The same as 1565-83A, except that the $CaCO_3$ was sourced from Pfizer.

Formula CL 1565-73

See Example 2, Alkaline tablet.

Formula CL 1565-82

See Example 3, Alkaline tablet.

The acid consuming capacity (ACC value) for each of the aforesaid alkaline tablets were as follows:

CL 1565-82	4.1 meq
CL 1565-73	4.3 meq
CL 1565-83A	3.75 meq
CL 1565-83B	4.1 meq

Procedure:

A Radiometer pH stat, Model 79752 was used for this work. The alkaline material is added to the sample cup along with 40 ml of 0.01N HCl. The apparatus is set to maintain the pH at 2. The instrument will automatically add acid (0.2N) to keep the pH constant at 2. As the antacid reacts it will attempt to raise the solution pH. A strip

chart recorder plots the addition of acid versus time. An antacid which reacts rapidly will cause the acid to be added rapidly, resulting in a steep slope for the recorder plot.

Tests:

To determine the rate of reaction of the respective alkaline tablets with acid, two measurements were made. The first measurement was the initial slope of the curve that is generated by plotting the volume of test acid added to the reaction beaker over time to maintain the constant pH (pH 2). The other measurement is the time in minutes that it takes to consume 50% of the acid consuming capacity of the test alkaline tablet. Five runs were made with each of the test alkaline tablets. The results of these runs are reported in Table I below:

TABLE I

	CL 1565-73 190 mg w/citrophosphate		CL 1565-82 193 mg w/citrophosphate		CL 1565-83A 177 mg without citrophosphate		CL 1565-83 without citric acid	
	slope	T min 50% meq	slope	T min 50% meq	slope	T min 50% meq	slope	T min 50% meq
	21.4	0.6	23.3	0.5	10.1	1.9	9.1	2.0
	20.5	0.6	24.7	0.6	11.1	1.7	8.8	2.0
	22.1	0.5	20.3	0.6	7.9	2.1	9.7	2.1
	22.8	0.6	23.1	0.6	10.2	1.8	8.1	2.0
	20.0	0.6	21.7	0.6	9.2	2.0	8.0	2.1
M =	21.4	0.6 ± 0	22.6	0.6	9.7	1.9	8.7	2.0
			± 1.7	± 0	± 1.2	± 1.2	± 0.7	± 0.1
			CR=0.9		CR=2.2		CR=2.5	

The "CR" value reported in Table I is the comparison ratio and is obtained from the following formula:

$$\text{CR - comparison ratio} = \frac{\text{Slope (M) standard}}{\text{Slope (M) sample}}$$

where the mean slope value (M) for CL 1565-73 is taken as the standard. This is introduced to minimize the variation in results that may be due to variations in stirring.

An examination of this Table will show that by all the criteria, the reaction rate of the alkaline tablets containing the citric acid and monobasic sodium phosphate i.e. Formulas CL 1565-73 and CL 1565-82 was greater when compared with those alkaline compositions that did not contain these materials.

WHAT IS CLAIMED IS:

1. A compressed and formed alkaline component adapted for use in conjunction with an acetylsalicylic acid (ASA) containing composition so as to provide a buffered ASA product; said compressed alkaline component comprising an effective buffering amount of an alkaline material selected from the group consisting of calcium carbonate, magnesium carbonate, a magnesium oxy component and mixtures; said magnesium oxy component being selected from the group consisting of magnesium oxide, magnesium hydroxide and a combination of magnesium oxide and magnesium hydroxide; said compressed alkaline component also having incorporated therein citric acid and monobasic sodium phosphate in sufficient quantities to enhance the acid neutralizing reaction rate of said alkaline component.

2. A compressed and formed alkaline component according to Claim 1 in which the total alkaline material in said alkaline component is in the range of from about 35% to about 95% by weight based on the total weight of said alkaline component.

3. A compressed and formed alkaline component according to Claim 2 in which the alkaline material in said component is in the range of from about 75% to about 95% by weight based on the total weight of said alkaline component.

4. A compressed and formed alkaline component according to Claim 1 containing at least one of said alkaline materials and in which the various ingredients are present in said compressed alkaline component within the following ranges based on the total weight of said compressed alkaline component:

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calcium carbonate	from about 0% to about 95%
magnesium carbonate	from about 0% to about 95%
magnesium oxy component	from about 0% to about 95%
citric acid	from about 1% to about 5%
monobasic sodium phosphate	from about 1% to about 5%

5. A compressed and formed alkaline component according to Claim 1 containing at least two of said alkaline materials and in which the various ingredients are present in said compressed alkaline component within the following ranges based on the total weight of said compressed alkaline component:

calcium carbonate	from about 0% to about 75%
magnesium carbonate	from about 0% to about 35%
magnesium oxy component	from about 0% to about 75%
citric acid	from about 1% to about 5%
monobasic sodium phosphate	from about 1% to about 5%

6. A compressed and formed alkaline component according to Claim 1 containing at least three of said alkaline materials in which the various ingredients are present in said compressed alkaline component within the following ranges based on the total weight of said compressed alkaline component:

calcium carbonate	from about 20% to about 75%
magnesium carbonate	from about 5% to about 35%
magnesium oxy component	from about 10% to about 75%
citric acid	from about 1% to about 5%
monobasic sodium phosphate	from about 1% to about 5%

7. A unit dosage form comprising a compressed and formed alkaline component and an ASA containing composition; said compressed alkaline component comprising an effective buffering amount of an alkaline material selected from the group consisting of calcium carbonate, magnesium carbonate, a magnesium oxy component and mixtures thereof; said magnesium oxy component being selected from the group consisting of magnesium oxide, magnesium hydroxide and a combination of magnesium oxide and magnesium hydroxide; said compressed alkaline component also having incorporated therein citric acid and monobasic sodium phosphate in sufficient quantities to enhance the acid neutralizing reaction rate of said alkaline component; said ASA being present in said dosage form in therapeutically effective amounts.

8. A unit dosage form according to Claim 7 in the form of a capsule containing the compressed alkaline component in the form of at least one tablet or pellet and the ASA in the form of a powder or granulation.

9. A unit dosage form according to Claim 7 in the form of a multi-layered tablet, said compressed alkaline component comprising one layer of said tablet and said ASA being contained in another layer of said tablet.

10. A unit dosage form according to Claims 7, 8 or 9 in which said alkaline material is present in said dosage form at a level of from about 20% to about 150% by weight based on the weight of the ASA in said unit dosage form.

11. A unit dosage form according to Claims 7, 8, or 9 in which the compressed alkaline component contains at least one of said alkaline materials and in which the various ingredients are present in said compressed alkaline component

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within the following ranges based on the total weight of said compressed alkaline component:

calcium carbonate	from about 0% to about 95%
magnesium carbonate	from about 0% to about 95%
magnesium oxy component	from about 0% to about 95%
citric acid	from about 1% to about 5%
monobasic sodium phosphate	from about 1% to about 5%

12. A unit dosage form according to Claims 7, 8, or 9 in which the compressed alkaline component contains at least two of said alkaline materials and in which the various ingredients are present in said compressed alkaline component within the following ranges based on the total weight of said compressed alkaline component:

calcium carbonate	from about 0% to about 75%
magnesium carbonate	from about 0% to about 35%
magnesium oxy component	from about 0% to about 75%
citric acid	from about 1% to about 5%
monobasic sodium phosphate	from about 1% to about 5%

13. A unit dosage form according to Claims 7, 8, or 9 in which the compressed alkaline component contains at least three of said alkaline materials and in which the various ingredients are present in said compressed alkaline component within the following ranges based on the total weight of said compressed alkaline component:

calcium carbonate	from about 20% to about 75%
magnesium carbonate	from about 5% to about 35%
magnesium oxy component	from about 10% to about 75%
citric acid	from about 1% to about 5%
monobasic sodium phosphate	from about 1% to about 5%

14. A unit dosage form comprising a capsule containing an alkaline component in the form of one or more tablets and an ASA mixture in powder or granular form; said alkaline component comprising a mixture containing calcium carbonate, magnesium carbonate and a magnesium oxy component selected from the group consisting of magnesium oxide, magnesium hydroxide and a mixture of magnesium oxide and magnesium hydroxide and also having incorporated therein citric acid and monobasic sodium phosphate; said alkaline component being present in said capsule at a level of from about 150 mg to about 400 mg per capsule and the ASA being present in said capsule at a level of from about 81 mg to about 650 mg, the relative proportions of the ingredients in said alkaline component based on the total weight of said alkaline component being as follows:

calcium carbonate	from about 20% to about 75%
magnesium carbonate	from about 5% to about 35%
magnesium oxy component	from about 10% to about 75%
citric acid	from about 1% to about 5%
monobasic sodium phosphate	from about 1% to about 5%

15. A unit dosage form according to Claim 14 in which the ASA is present in said capsule at a level from about 325 to about 650 mg. per capsule.

16. A unit dosage form comprising a multi-layered tablet containing an alkaline layer and an ASA layer; said alkaline layer comprising a mixture containing calcium carbonate, magnesium carbonate and a magnesium oxy component selected from the group consisting of magnesium oxide, magnesium hydroxide and a mixture of magnesium oxide and magnesium hydroxide and also having incorporated therein

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citric acid and monobasic sodium phosphate, said alkaline material being present in said alkaline layer at a level of from about 150 mg to about 400 mg per unit dosage form and the ASA being present in said capsule at a level of from about 81 mg to about 650 mg per unit dosage form, the relative portions of the ingredients in said alkaline layer based on the total weight of said alkaline layer being as follows:

calcium carbonate	from about 20% to about 75%
magnesium carbonate	from about 5% to about 35%
magnesium oxy component	from about 10% to about 75%
citric acid	from about 1% to about 5%
monobasic sodium phosphate	from about 1% to about 5%

17. A unit dosage form according to Claim 16 in which the ASA is present in said unit dosage form at a level of from about 325 mg to about 650 mg per unit dosage form.

18. A process for forming a compressed alkaline component which comprises forming a dry mix comprising calcium carbonate, magnesium carbonate and a magnesium oxy component selected from the group consisting of magnesium oxide, magnesium hydroxide and a combination of magnesium oxide and magnesium hydroxide, wetting said mixture with a granulating liquid containing citric acid and monobasic sodium phosphate, granulating said wetted mixture and then compressing said granulated material to form a compressed alkaline component.

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19. A process according to Claim 18 in which said citric acid is present in said granulating liquid at a level in the range of from about 1% to about 5% by weight based on the total weight of the granulating liquid and said monobasic sodium phosphate is present in said granulating liquid at a level in the range of from about 1% to about 5% by weight based on the total weight of granulating liquid.

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SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente